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# Smoking addiction and the risk of upper aerodigestive tract cancer in a multicenter case-control study

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## Abstract

While previous studies on tobacco and alcohol and the risk of upper aerodigestive tract (UADT) cancers have clearly shown dose-response relations with the frequency and duration of tobacco and alcohol, studies on addiction to tobacco smoking itself as a risk factor for UADT cancer have not been published, to our knowledge. The aim of this report is to assess whether smoking addiction is a risk factor for UADT squamous cell carcinoma (SCC) risk in the multicenter case-control study (ARCAGE) in Western Europe, independent of tobacco smoking. The analyses included 1,586 ever smoking UADT SCC cases (761 oral cavity/oropharynx, 623 hypopharynx/larynx, 127 esophagus, and 75 overlapping oral cavity/pharynx) and 1,260 ever smoking controls. The addiction variables included first cigarette after waking up, difficulty refraining from smoking in places where it is forbidden, and cigarettes per day. Odds ratios (OR) and 95% confidence intervals (95% CI) for UADT cancers with addiction variables were estimated with unconditional logistic regression, adjusting for center, age, sex, education level, alcohol consumption, and tobacco smoking. Among current smokers, 76.47% of cases were categorized in the highest addiction level, whereas 54.69% of controls were in that category. The participants who smoked their first cigarette within 5 minutes of waking up were two times more likely to develop UADT SCC (OR=2.22, 95% CI 1.57-3.15) than those who smoked 60 minutes after waking up. A higher modified Fagerström score, reflecting greater tobacco smoking addiction, was associated with an increased risk of UADT SCC among current smokers, but not among former smokers. These results may be consistent with a residual effect of smoking that was not captured by the questionnaire responses (on smoking intensity and smoking duration) alone.

## Introduction

The 8-item Fagerström Tolerance Questionnaire (FTQ) is a widely used assessment tool for smoking addiction (1). The FTQ was originally designed to assess physical dependence and tolerance to tailor treatments to smokers with different levels of dependence (2). The Fagerström test for nicotine dependence (FTND) is a short version with six questions of FTQ (3), including time to first cigarette after waking up, difficulty refraining from smoking in places where it is forbidden, hate giving up the first cigarette in the morning compared to all the other cigarettes, cigarettes smoked per day, more frequent smoking during the first hour after waking up than the rest of the day, and smoking even when ill and in bed most of the day. This scale has been widely used because it is convenient for clinical and research purposes as a self-administered measure (2). To date, in the only published study on Fagerström scores and cancer risk, Deheinz et al. reported an association between Fagerström Tolerance Questionnaire score  $\geq 7$  and overall cancer risk (adjusted OR=3.45, 95% CI 1.52-7.83,  $p=0.003$ ) in a smoking cessation group (4). A total of 54 cases with a variety of histology and cancer sites were included in the study. Recently, Muscat et al. reported an association (OR=1.59, 95% CI 1.19-2.11 for 1-30 minutes, compared to >60 minutes) between time to first cigarette after waking and oral and pharyngeal cancer risk in a case-control study (5).

Tobacco smoking and alcohol drinking behaviors often occur together (6). Among US adults, 82.5% of current alcohol drinkers were ever tobacco smokers, whereas 77.9% of former alcohol drinkers were ever tobacco smokers (7). Alcohol dependence and tobacco addiction are also correlated (8). Individuals with alcohol dependence are three times more likely than the US general population to be smokers, whereas people with tobacco addiction are four times more likely than the general population to have alcohol dependence (8). Approximately 46 million adults in the US were both alcohol drinkers and tobacco smokers in 2006; and 6.2 million adults reported dependence on both alcohol and tobacco (9). Tobacco smoking and alcohol drinking are well established risk factors for UADT SCC (10); (11).

While previous studies on tobacco and alcohol on the risk of UADT cancers have clearly shown dose-response relations with the frequency and duration of tobacco and alcohol, studies on addiction to tobacco itself as a risk

factor for UADT cancer have not been published, to our knowledge. In addition to tobacco smoking, it is likely that smoking addiction is correlated with alcohol drinking, and possibly with socioeconomic status, sex, or risky sexual behaviors (12); (13); (14), all of which could act as potential confounders for assessing the relationship between smoking addiction and UADT cancer risk. There is also evidence that questionnaire information on smoking captures only a part of the relationship between smoking and cancer (15). We suspect that tobacco addiction measures may provide more information on the smoking and UADT cancer relationship than the usual smoking questions in the surveys.

The aim of this report is to assess whether smoking addiction is a risk factor for UADT SCC risk in a multicenter case-control study (ARCAGE) in Western Europe, independent of tobacco smoking. This is the first study investigating the association between smoking addiction and UADT SCC risk with stratification by tobacco smoking.

## **Methods**

### Study Population

Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) is a multicenter case-control study with recruitment in 14 centers from 10 European countries (Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain and United Kingdom). The study was approved by the ethical review board of IARC, as well as the respective local boards in the participating centers. All subjects provided written informed consent for their participation in the study.

Details on the study design have been provided previously (16). Briefly, incident cases were identified from participating hospitals and were histologically or cytologically confirmed. Eligible cases were classified under specific ICD-O codes (C00, C01, C02, C03, C04, C05, C06, C09, C10, C12, C13, C14.0, C14.8, C15.0, C15.3, C15.4, C15.5, C15.8, C15.9, and C32), (16) including cancer of the oral cavity, pharynx (excluding nasopharynx), larynx and esophagus. Recruitment was conducted from 2002 to 2005 for all centers, except for the French center, where recruitment was conducted during 1987 to 1992. Cases were identified by participating hospitals within 6 months of diagnosis. Six cases were excluded from the analysis due to missing

information on age, sex or education. Among the 2,286 UADT cancer cases, 92.3% of the cases were squamous cell carcinoma (SCC). We focused our analysis on cases with SCC histology, since the etiology of UADT cancer of other histologies may differ. We also included only ever tobacco smokers, since tobacco smoking addiction was assessed only in people who smoked. The Paris center data were not included because tobacco smoking addiction information was not collected at this center. Of the 1,586 ever smoking UADT SCC cases in the remaining centers, 761 were oral cavity/oropharyngeal cancers, 623 were hypopharyngeal/laryngeal cancer cases, 127 were esophageal cancer cases and 75 were overlapping oral cavity/pharyngeal cancer cases (Table 1).

In each center, controls were frequency-matched to cases by sex, age, and referral (or residence) area. In the UK centers, population controls were randomly chosen from the same family medical practice list as the corresponding cases. In the remaining centers, hospital controls with a recently diagnosed disease were used, and admission diagnoses related to alcohol, tobacco or dietary practices were excluded. Eligible control admission diagnosis included 1) endocrine and metabolic 2) genitor-urinary 3) skin, subcutaneous tissue, and musculoskeletal, 4) gastro-intestinal, 5) circulatory, 6) ear, eye and mastoid, and 7) nervous system diseases, as well as 8) plastic surgery cases, and 9) trauma patients. The proportion of controls within a specific diagnostic group did not exceed 33% of the total. In the UK centers, population controls were recruited from a randomly selected list of ten controls for every case, matched by age, sex, and same family medical practice. After excluding six controls due to missing information on age, sex or education and including ever smokers only, 1,260 ever smoking controls were included in the analysis. In the Paris center, smoking addiction information was not collected, so the data were not included in the analysis.

Cases and controls underwent identical interviews during which they completed a lifestyle questionnaire. The questionnaire included information on socio-demographic variables, as well as detailed smoking and alcohol drinking histories. The participation rates ranged from 35% to 100% for cases and from 26% to 100% for controls. The UK centers with population-based recruitment had the lower participation rates, compared to the other centers.

## Statistical Analysis

For the assessment of main effects of smoking addiction, all ever smoking UADT cancer cases were analyzed both together and stratified by cancer subsite. The distribution of cases and controls by age, center, sex, education, and histology was examined. Odds ratios (OR) and 95% confidence intervals (95% CI) for UADT cancers with addiction variables (first cigarette after waking and difficulty to refrain from smoking) were estimated with unconditional logistic regression, adjusting for center, age (categories shown in Table 1), sex, education level (categories shown in Table 1), and alcohol consumption (intensity as a continuous variable and duration as a categorical variable), tobacco smoking pack-years (continuous).

Ever smokers were defined as individuals who ever smoked cigarettes, cigars, pipes or any tobacco products at least once a week for a year. Former smokers were defined as smokers who had stopped for at least 12 months. The different types of tobacco smoking were converted to cigarette equivalents (1 cigar = 4 cigarettes and 1 pipe = 3.5 cigarettes). Heatherton et al. modified the original Fagerström score to a six-item questionnaire and suggested that with limited resources it might be most effective to score only the time to first cigarette after waking up and number of cigarettes per day (3). In our analysis, modified Fagerström scores (range 0-7) were calculated by summing the scores from the three variables available in ARCAGE: time to first cigarette after waking up (after 60 minutes=0, within 31-60 minutes=1, within 6-30 minutes=2, within 5 minutes=3), difficulty to refrain from smoking in places where it is forbidden (no difficulties=0, difficulties=1), and intensity of smoking (<10 cigarettes/day=0, >10-20 cigarettes/day=1, >20-30 cigarettes/day=2, >30 cigarettes/day=3). Higher scores indicate more addiction while lower scores suggest less addiction.

Stratified analyses by cigarettes per day of smoking and cumulative alcohol drinking were performed to evaluate whether the associations observed with time to first cigarette after waking were modified by the



amount of tobacco use. Statistical analyses were conducted using the SAS 9 statistical software. All p-values were two-sided.

## Results

In this analysis, we included 1,586 UADT SCC cases and 1,260 controls who ever smoked tobacco (Table 1). As expected, there were a higher proportion of the highly educated individuals among the controls (8.17%) than the cases (4.60%). In our initial assessment of the three components for the Fagerström test among current smokers, time to first cigarette after waking up (OR ~1.6-2.3) and number of cigarettes smoked per day (OR ~1.6-2.3) showed similar associations with UADT SCC risk, but stronger than difficulty to refrain from smoking at places where smoking is prohibited (OR ~0.74). Among the current smoking controls, a higher proportion of individuals with lower education levels had higher Fagerström scores (3-7) ( $p=0.002$ ; data not shown), whereas men were more likely to have a higher Fagerström score than women ( $p=0.046$ ; data not shown). Among current smokers, the mean 3-item Fagerström scores ( $\pm$ Standard deviation) were  $3.70\pm1.76$  for cases and  $2.77\pm1.90$  for controls; among former smokers, the mean scores were  $2.93\pm2.03$  for cases and  $2.35\pm2.03$  for controls (data not shown in table).

Among current smokers, an inverse dose-response trend was detected between time to first cigarette after waking up and UADT SCC risk ( $p<0.001$ ) (Table 2). No association was observed with difficulties of refraining from smoking at a place where smoking is forbidden (results not shown). The participants who smoked the first cigarette within 5 minutes were two times more likely to develop UADT SCC (OR=2.22, 95% CI 1.57-3.15) than those who smoked 60 minutes after waking up. However, a dose-response trend between time to first cigarette and UADT SCC risk was not observed among former smokers ( $p=0.99$ ). A higher modified Fagerström score, reflecting greater tobacco smoking addiction, was associated with an increased risk of UADT SCC among current smokers, but not among former smokers. We did not observe any apparent differences across the UADT subsites for relationship between smoking addiction and cancer risk among the current smokers. The relationship between smoking addiction and UADT SCC remained similar with further adjustment by fruit and vegetable consumption (data not shown).

When stratified by sex, time to first cigarette after waking up was associated with the risk of UADT SCC among men (adjusted OR=1.69, 95% CI 1.26-2.25 for within 5 minutes), but not among women (adjusted OR=1.38, 95% CI 0.72-2.64 for within 5 minutes,  $p$  for trend=0.086) (Table 3). Among women, an association with smoking 6-30 minutes after waking up (OR=2.23, 95% CI 1.30-3.83) was detected. Overall, dose-response trends between modified Fagerström scores and UADT SCC risk were detected for both men ( $p<0.001$ ) and women ( $p=0.006$ ).

Among current smokers who smoked <10 cigarettes per day, smoking within a short time after waking up was associated with an increased risk of UADT SCC (Table 4). We did not show the results for esophageal cancer due to sparse data. For former smokers, after stratifying by smoking intensity, smoking within a short time after waking up was not associated with the risk of UADT SCC regardless of smoking intensity (data not shown). In addition to stratified analyses, interaction terms between modified Fagerström score and smoking intensity or cumulative alcohol drinking were assessed but none were detected ( $p=0.27$  for cigarettes smoked per day and  $p=0.78$  for cumulative alcohol drinking among current smokers; data not shown).

When stratified by cumulative alcohol drinking, we detected an association between modified Fagerström scores and UADT SCC risk among current smokers even among individuals with low cumulative alcohol drinking (<1,000 drinks in lifetime) (OR=21.17, 95% CI 3.50-128.00 for a score of 3-7,  $p<0.001$ ) although the precision was low (Table 5). We were not able to examine never drinkers due to sparse data.

## Discussion

Our study showed that among current smokers, smoking addiction was associated with UADT SCC risk. Similar to the previous study on all cancers by Deheinz et al. (4), in our study we found an effect size of 3.83 (95%CI=2.56-5.73) for UADT SCC risk with a modified Fagerström score of 3-7. Furthermore, the ORs for UADT cancers ranged 1.65-2.22 for <60 minutes to first cigarette after waking when compared to >60 minutes, which is similar to the associations reported by Muscat et al. for head and neck cancer (5). The association between time to first cigarette after waking and UADT SCC risk did not appear to be due to reported heavier smoking. If smoking addiction increased the risk of UADT SCC because of heavier smoking,

then we would expect that the individuals who smoked >20 cigarettes per day would have the greatest risk for this association. This may imply the misclassification of smoking via questionnaires. In our study, we observed associations between time to first cigarette and UADT SCC risk regardless of smoking intensity. Similarly, our stratified analysis by cumulative alcohol drinking supported the relationship between first cigarette after waking up and UADT SCC independent of cumulative alcohol drinking.

While we observed associations between addiction measures and UADT SCC risk among current smokers, these associations were not observed among past smokers. We explored the possibility of reverse causality, where perhaps the past smokers were individuals who were less addicted to begin with and thus were able to quit successfully. Though the crude mean Fagerström scores among current smoking controls were slightly higher (2.77) compared to past smokers (2.35), the difference was not statistically significant. Perhaps the association between addiction and UADT cancer is more moderate among past smokers than current smokers, and we did not have enough statistical power to detect associations.

Based on our results, the questionnaire information on tobacco smoking and alcohol drinking could not fully explain the observed association between smoking addiction and UADT SCC risk. We observed correlation of addiction with education and with gender, both of which are potential confounding factors. However, we adjusted on these factors and the association between smoking addiction and UADT SCC was still observed. Though residual confounding from these factors is still a possibility, we do not expect that residual confounding can fully explain our observed addiction-UADT SCC risk association. Another possible pathway may be that smoking addiction might be related to risky sexual behavior via the human papillomavirus (HPV) pathway to UADT SCC. HPV is a risk factor mainly for oropharyngeal cancers (17), and the interaction between HPV and tobacco smoking may vary by subsites (18). However, we observed similar addiction-cancer associations with oral cavity/oropharynx, hypopharyngeal/laryngeal, and esophageal cancers. Thus, we do not believe that the HPV pathway explains the observed association. The detected addiction-cancer association may be an indication of the smoking-cancer association being stronger than that observed on questionnaire data on smoking intensity.

Our study had several limitations including potential recall bias, residual confounding and sparse data. The addiction and lifestyle information was self-reported in interviews. With the knowledge of their cancer status for the UADT cancer patients, the cases might have recalled various exposures differently from the controls. This limitation might have impact on the assessment of smoking intensity, but perhaps less so for time to first cigarette after waking up since a relationship between time to first cigarette after waking up and UADT SCC risk has not been established. There could be residual confounding by tobacco smoking and alcohol drinking due to inability to stratify by finer categories of low tobacco smoking and alcohol drinking intensity or lifetime amount. Although we performed stratified analyses, sparse data were a limitation for UADT subsites, especially for esophageal cancer and for finer strata of very low tobacco smoking or alcohol drinking. Finally, we utilized only three components of the FTND to assess smoking addiction in ARCAGE because the other three components were not available in our study. As mentioned earlier, the two items (time to first cigarette after waking up and number of cigarettes smoked per day) account for the majority of variance for FTQ scores (3). Thus, we believe our use of a modified Fagerström score was reasonable.

The possible mechanisms of an effect of the addiction score in addition to that of tobacco smoking as measured by questionnaire are complicated by the fact that cigarettes smoked per day is included in both approaches. Thus, we also attempted to focus on the other main component (time to first cigarette after waking) of the score in our analysis. We observed that time to first cigarette after waking was associated with UADT SCC risk regardless of the number of cigarettes smoked per day. The investigation may be whether the score corrects (at least in part) the misclassification of smoking (i.e., weak smokers with strong dependence are in fact misclassified heavy smokers), or whether nicotine dependence is a marker of susceptibility to tobacco carcinogenesis (i.e., more dependent smokers are at higher risk than less dependent smokers given the same amount of tobacco smoking). The latter can happen through metabolic pathways that are in common to nicotine and tobacco carcinogens, such as tobacco-specific nitrosamines (TSN), which are derivatives of nicotine. The latter explanation might be explored through an analysis of *CYP2A6*, *CHRNA5-A3-B4* (19) and other genes involved in nicotine metabolism, in particular those involved in the formation of TSN.

This is the first study to examine the relationship between smoking addiction and UADT SCC risk in a large multicenter case-control study. We observed that smoking addiction, especially time to first cigarette after waking up was associated with UADT SCC risk, independent of heavy smoking or alcohol drinking behaviors. These results may be consistent with a residual effect of smoking that was not captured by the questionnaire responses (on smoking intensity and smoking duration) alone. In summary, the addiction-cancer association suggests that inclusion of addiction information when accounting for smoking effect through questionnaire information is important.

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**Table 1. Demographic characteristics of the UADT SCC cases and controls (ever smokers only)**

|                  |                                | Cases        |         | Controls     |          |
|------------------|--------------------------------|--------------|---------|--------------|----------|
|                  |                                | n            | (%)     | n            | (%)      |
| <b>Total</b>     |                                | <b>1,586</b> |         | <b>1,260</b> |          |
| <b>Center</b>    |                                |              |         |              |          |
|                  | Prague                         | 146          | (9.21)  | 118          | (9.37)   |
|                  | Bremen                         | 263          | (16.58) | 234          | (18.57)  |
|                  | Athens                         | 187          | (11.79) | 134          | (10.63)  |
|                  | Aviano                         | 119          | (7.50)  | 83           | (6.59)   |
|                  | Padova                         | 113          | (7.12)  | 74           | (5.87)   |
|                  | Turin                          | 125          | (7.88)  | 130          | (10.32)  |
|                  | Dublin                         | 29           | (1.83)  | 13           | (1.03)   |
|                  | Oslo                           | 116          | (7.31)  | 115          | (9.13)   |
|                  | Edinburgh                      | 82           | (5.17)  | 47           | (3.73)   |
|                  | Manchester                     | 130          | (8.20)  | 118          | (9.37)   |
|                  | Newcastle                      | 58           | (3.66)  | 67           | (5.32)   |
|                  | Barcelona                      | 172          | (10.84) | 95           | (7.54)   |
|                  | Zagreb                         | 46           | (2.90)  | 32           | (2.54)   |
| <b>Age</b>       |                                |              |         |              |          |
|                  | <40 years                      | 25           | (1.58)  | 52           | (4.13)   |
|                  | 40-44 years                    | 57           | (3.59)  | 64           | (5.08)   |
|                  | 45-49 years                    | 157          | (9.90)  | 98           | (7.78)   |
|                  | 50-54 years                    | 252          | (15.89) | 185          | (14.68)  |
|                  | 55-59 years                    | 327          | (20.62) | 238          | (18.89)  |
|                  | 60-64 years                    | 273          | (17.21) | 183          | (14.52)  |
|                  | 65-69 years                    | 232          | (14.63) | 188          | (14.92)  |
|                  | 70-74 years                    | 158          | (9.96)  | 139          | (11.03)  |
|                  | 75+ years                      | 105          | (6.62)  | 113          | (8.97)   |
|                  | p-value                        | <0.001       |         |              |          |
| <b>Sex</b>       |                                |              |         |              |          |
|                  | Men                            | 1319         | (83.17) | 1026         | (81.43)  |
|                  | Women                          | 267          | (16.83) | 234          | (18.57)  |
|                  | p-value                        | 0.227        |         |              |          |
| <b>Education</b> |                                |              |         |              |          |
|                  | Finished primary school/worker | 584          | (36.82) | 312          | (24.76)  |
|                  | Finished further school/clerks | 929          | (58.58) | 845          | (67.06)  |
|                  | University degree/Manager      | 73           | (4.60)  | 103          | (8.17)   |
|                  | p-value                        | <0.001       |         |              |          |
| <b>Subsite</b>   |                                |              |         |              |          |
|                  | Controls                       |              |         | 1260         | (100.00) |
|                  | Oral/Oropharynx                | 761          | (47.98) |              |          |
|                  | Hypopharynx/Larynx             | 623          | (39.28) |              |          |
|                  | Esophagus                      | 127          | (8.01)  |              |          |
|                  | Overlapping                    | 75           | (4.73)  |              |          |



**Table 2. Smoking addiction and UADT SCC risk**

|  | UADT |     |      |                 | Oral & oropharynx |     |      |                 |
|--|------|-----|------|-----------------|-------------------|-----|------|-----------------|
|  | Ca   | Co  | OR   | 95% CI          | Ca                | Co  | OR   | 95% CI          |
| <b>Current smokers</b>                 |      |     |      |                 |                   |     |      |                 |
| <b>First cigarette after waking up</b> |      |     |      |                 |                   |     |      |                 |
| after 60 minutes                       | 160  | 168 | 1.00 |                 | 85                | 168 | 1.00 |                 |
| within 31-60 minutes                   | 168  | 98  | 1.65 | ( 1.16 - 2.34 ) | 84                | 98  | 1.68 | ( 1.10 - 2.57 ) |
| 6-30 minutes                           | 449  | 180 | 2.11 | ( 1.56 - 2.86 ) | 209               | 180 | 1.94 | ( 1.35 - 2.79 ) |
| within 5 minutes                       | 368  | 109 | 2.22 | ( 1.57 - 3.15 ) | 188               | 109 | 2.52 | ( 1.68 - 3.78 ) |
| Ptrend                                 |      |     |      | <0.001          |                   |     |      | <0.001          |
| <b>Modified Fagerström</b>             |      |     |      |                 |                   |     |      |                 |
| 0                                      | 50   | 86  | 1.00 |                 | 30                | 86  | 1.00 |                 |
| 1-2                                    | 219  | 165 | 2.06 | ( 1.34 - 3.15 ) | 108               | 165 | 1.72 | ( 1.03 - 2.88 ) |
| 3-7                                    | 874  | 303 | 3.83 | ( 2.56 - 5.73 ) | 427               | 303 | 3.42 | ( 2.11 - 5.55 ) |
| Ptrend                                 |      |     |      | <0.001          |                   |     |      | <0.001          |
| <b>Former smokers</b>                  |      |     |      |                 |                   |     |      |                 |
| <b>First cigarette after waking up</b> |      |     |      |                 |                   |     |      |                 |
| after 60 minutes                       | 125  | 303 | 1.00 |                 | 62                | 303 | 1.00 |                 |
| within 31-60 minutes                   | 88   | 114 | 1.54 | ( 1.05 - 2.24 ) | 42                | 114 | 1.56 | ( 0.96 - 2.53 ) |
| 6-30 minutes                           | 96   | 153 | 0.97 | ( 0.66 - 1.41 ) | 44                | 153 | 0.94 | ( 0.57 - 1.56 ) |
| within 5 minutes                       | 87   | 100 | 1.09 | ( 0.71 - 1.68 ) | 29                | 100 | 0.90 | ( 0.50 - 1.62 ) |
| Ptrend                                 |      |     |      | 0.998           |                   |     |      | 0.588           |
| <b>Modified Fagerström</b>             |      |     |      |                 |                   |     |      |                 |
| 0                                      | 53   | 164 | 1.00 |                 | 30                | 164 | 1.00 |                 |
| 1-2                                    | 125  | 216 | 1.31 | ( 0.86 - 1.98 ) | 64                | 216 | 1.35 | ( 0.80 - 2.28 ) |
| 3-7                                    | 217  | 286 | 1.23 | ( 0.81 - 1.85 ) | 83                | 286 | 0.93 | ( 0.55 - 1.59 ) |
| Ptrend                                 |      |     |      | 0.482           |                   |     |      | 0.517           |

\*Adjusted for center, education, sex, age, alcohol drinking frequency and duration, and pack-years of smoking (duration of smoking for the Fagerström estimates)

**Table 2. Smoking addiction and UADT SCC risk (continued)**

|  | Hypopharynx & larynx |     |      |                 | Esophagus |     |      |                  |
|--|----------------------|-----|------|-----------------|-----------|-----|------|------------------|
|  | Ca                   | Co  | OR   | 95%<br>CI       | Ca        | Co  | OR   | 95%<br>CI        |
| <b>Current smokers</b>                 |                      |     |      |                 |           |     |      |                  |
| <b>First cigarette after waking up</b> |                      |     |      |                 |           |     |      |                  |
| after 60 minutes                       | 61                   | 168 | 1.00 |                 | 11        | 168 | 1.00 |                  |
| within 31-60 minutes                   | 60                   | 98  | 1.56 | ( 0.97 - 2.50 ) | 12        | 98  | 2.40 | ( 0.88 - 6.55 )  |
| 6-30 minutes                           | 178                  | 180 | 2.10 | ( 1.40 - 3.15 ) | 43        | 180 | 4.74 | ( 2.04 - 10.99 ) |
| within 5 minutes                       | 133                  | 109 | 1.77 | ( 1.11 - 2.81 ) | 18        | 109 | 2.25 | ( 0.83 - 6.06 )  |
| Ptrend                                 |                      |     |      | 0.005           |           |     |      | 0.022            |
| <b>Modified Fagerström</b>             |                      |     |      |                 |           |     |      |                  |
| 0                                      | 13                   | 86  | 1.00 |                 | 6         | 86  | 1.00 |                  |
| 1-2                                    | 83                   | 165 | 2.72 | ( 1.39 - 5.30 ) | 17        | 165 | 1.96 | ( 0.65 - 5.87 )  |
| 3-7                                    | 335                  | 303 | 4.72 | ( 2.50 - 8.93 ) | 61        | 303 | 3.41 | ( 1.24 - 9.40 )  |
| Ptrend                                 |                      |     |      | <0.001          |           |     |      | 0.009            |
| <b>Former smokers</b>                  |                      |     |      |                 |           |     |      |                  |
| <b>First cigarette after waking up</b> |                      |     |      |                 |           |     |      |                  |
| after 60 minutes                       | 47                   | 303 | 1.00 |                 | 13        | 303 | 1.00 |                  |
| within 31-60 minutes                   | 35                   | 114 | 1.48 | ( 0.86 - 2.53 ) | 8         | 114 | 2.09 | ( 0.70 - 6.21 )  |
| 6-30 minutes                           | 41                   | 153 | 1.06 | ( 0.62 - 1.82 ) | 8         | 153 | 0.75 | ( 0.23 - 2.44 )  |
| within 5 minutes                       | 50                   | 100 | 1.47 | ( 0.83 - 2.59 ) | 6         | 100 | 1.14 | ( 0.32 - 4.04 )  |
| Ptrend                                 |                      |     |      | 0.322           |           |     |      | 0.922            |
| <b>Modified Fagerström</b>             |                      |     |      |                 |           |     |      |                  |
| 0                                      | 17                   | 164 | 1.00 |                 | 4         | 164 | 1.00 |                  |
| 1-2                                    | 44                   | 216 | 1.15 | ( 0.60 - 2.19 ) | 15        | 216 | 3.80 | ( 1.01 - 14.26 ) |
| 3-7                                    | 111                  | 286 | 1.53 | ( 0.83 - 2.85 ) | 16        | 286 | 2.51 | ( 0.62 - 10.11 ) |
| Ptrend                                 |                      |     |      | 0.112           |           |     |      | 0.404            |

\*Adjusted for center, education, sex, age, alcohol drinking frequency and duration, and pack-years of smoking (duration of smoking for the Fagerström estimates)

**Table 3. Smoking addiction and UADT SCC risk, stratified by sex**

|  | Men |     |      |                 | Women |    |      |                 |
|--|-----|-----|------|-----------------|-------|----|------|-----------------|
|  | Ca  | Co  | OR   | 95% CI          | Ca    | Co | OR   | 95% CI          |
| <b>First cigarette after waking up</b> |     |     |      |                 |       |    |      |                 |
| after 60 minutes                       | 230 | 376 |      |                 | 55    | 95 |      |                 |
| within 31-60 minutes                   | 219 | 182 | 1.54 | ( 1.17 - 2.04 ) | 37    | 30 | 1.83 | ( 0.98 - 3.44 ) |
| 6-30 minutes                           | 447 | 277 | 1.56 | ( 1.21 - 2.02 ) | 98    | 56 | 2.23 | ( 1.30 - 3.83 ) |
| within 5 minutes                       | 392 | 167 | 1.69 | ( 1.26 - 2.25 ) | 63    | 42 | 1.38 | ( 0.72 - 2.64 ) |
| Ptrend                                 |     |     |      | <0.001          |       |    |      | 0.086           |
| <b>Modified Fagerström</b>             |     |     |      |                 |       |    |      |                 |
| 0                                      | 71  | 182 | 1.00 |                 | 32    | 68 | 1.00 |                 |
| 1-2                                    | 276 | 317 | 1.42 | ( 1.00 - 2.01 ) | 68    | 64 | 2.10 | ( 1.17 - 3.77 ) |
| 3-7                                    | 938 | 498 | 2.15 | ( 1.54 - 3.00 ) | 153   | 91 | 2.34 | ( 1.33 - 4.13 ) |
| Ptrend                                 |     |     |      | <0.001          |       |    |      | 0.006           |

\*Adjusted for center, education, sex, age, alcohol drinking frequency and duration and pack-years (duration of smoking for the Fagerström estimates)

**Table 4. Time to first cigarette after waking up among current smokers and UADT SCC risk, stratified by smoking intensity**

|                              | UADT overall |    |      |                 | Oral & oropharynx |    |      |                  | Hypopharynx & larynx |    |      |                  |
|------------------------------|--------------|----|------|-----------------|-------------------|----|------|------------------|----------------------|----|------|------------------|
|                              | Ca           | Co | OR   | 95% CI          | Ca                | Co | OR   | 95% CI           | Ca                   | Co | OR   | 95% CI           |
| <b>≤ 10 cigarette/day</b>    |              |    |      |                 |                   |    |      |                  |                      |    |      |                  |
| After 60 minutes             | 51           | 89 |      |                 | 30                | 89 |      |                  | 14                   | 89 |      |                  |
| Within 31-60 minutes         | 16           | 20 | 1.20 | ( 0.50 - 2.91 ) | 6                 | 20 | 0.72 | ( 0.21 - 2.45 )  | 5                    | 20 | 2.19 | ( 0.52 - 9.25 )  |
| Within 6-30 minutes          | 44           | 24 | 2.65 | ( 1.29 - 5.46 ) | 22                | 24 | 2.56 | ( 1.05 - 6.21 )  | 13                   | 24 | 4.64 | ( 1.21 - 17.81 ) |
| Within 5 minutes             | 17           | 8  | 2.84 | ( 0.98 - 8.22 ) | 11                | 8  | 5.52 | ( 1.58 - 19.25 ) | 5                    | 8  | 5.52 | ( 0.61 - 49.81 ) |
| Ptrend                       |              |    |      | 0.004           |                   |    |      | 0.004            |                      |    |      | 0.015            |
| <b>11-20 cigarettes/day</b>  |              |    |      |                 |                   |    |      |                  |                      |    |      |                  |
| After 60 minutes             | 79           | 60 |      |                 | 37                | 60 |      |                  | 36                   | 60 |      |                  |
| Within 31-60 minutes         | 95           | 63 | 1.23 | ( 0.75 - 2.00 ) | 50                | 63 | 1.41 | ( 0.78 - 2.56 )  | 31                   | 63 | 0.92 | ( 0.48 - 1.77 )  |
| Within 6-30 minutes          | 222          | 96 | 1.78 | ( 1.14 - 2.77 ) | 114               | 96 | 1.85 | ( 1.08 - 3.16 )  | 73                   | 96 | 1.59 | ( 0.90 - 2.82 )  |
| Within 5 minutes             | 122          | 47 | 1.76 | ( 1.05 - 2.94 ) | 64                | 47 | 2.05 | ( 1.12 - 3.78 )  | 37                   | 47 | 1.23 | ( 0.62 - 2.41 )  |
| Ptrend                       |              |    |      | 0.009           |                   |    |      | 0.012            |                      |    |      | 0.209            |
| <b>&gt;20 cigarettes/day</b> |              |    |      |                 |                   |    |      |                  |                      |    |      |                  |
| After 60 minutes             | 30           | 19 |      |                 | 18                | 19 |      |                  | 11                   | 19 |      |                  |
| Within 31-60 minutes         | 57           | 15 | 2.71 | ( 1.13 - 6.48 ) | 28                | 15 | 2.60 | ( 0.93 - 7.32 )  | 24                   | 15 | 3.03 | ( 1.01 - 9.12 )  |
| Within 6-30 minutes          | 183          | 60 | 2.21 | ( 1.08 - 4.52 ) | 73                | 60 | 1.56 | ( 0.67 - 3.66 )  | 92                   | 60 | 2.97 | ( 1.17 - 7.53 )  |
| Within 5 minutes             | 229          | 54 | 2.41 | ( 1.15 - 5.02 ) | 113               | 54 | 2.37 | ( 1.00 - 5.66 )  | 91                   | 54 | 2.23 | ( 0.86 - 5.79 )  |
| Ptrend                       |              |    |      | 0.108           |                   |    |      | 0.143            |                      |    |      | 0.401            |

\*Adjusted for center, education, sex, age, alcohol duration, and alcohol frequency

**Table 5. Smoking addiction and UADT SCC risk, stratified by cumulative alcohol drinking**

|                                     | Current smokers |     |       |                   | Former smokers |     |      |                  |
|-------------------------------------|-----------------|-----|-------|-------------------|----------------|-----|------|------------------|
|                                     | Ca              | Co  | OR    | 95% CI            | Ca             | Co  | OR   | 95% CI           |
| <b>&lt;1,000 drinks/lifetime</b>    |                 |     |       |                   |                |     |      |                  |
| <b>Modified Fagerström</b>          |                 |     |       |                   |                |     |      |                  |
| 0                                   | 4               | 18  | 1.00  |                   | 4              | 20  | 1.00 |                  |
| 1-2                                 | 14              | 21  | 10.92 | ( 1.73 - 69.08 )  | 8              | 31  | 1.65 | ( 0.24 - 11.43 ) |
| 3-7                                 | 47              | 39  | 21.17 | ( 3.50 - 128.00 ) | 10             | 22  | 3.43 | ( 0.42 - 28.06 ) |
| Ptrend                              |                 |     |       | <0.001            |                |     |      | 0.233            |
| <b>&gt;=1,000-&lt;10,000 drinks</b> |                 |     |       |                   |                |     |      |                  |
| <b>Modified Fagerström</b>          |                 |     |       |                   |                |     |      |                  |
| 0                                   | 22              | 31  | 1.00  |                   | 18             | 55  | 1.00 |                  |
| 1-2                                 | 57              | 53  | 1.31  | ( 0.62 - 2.79 )   | 29             | 62  | 1.32 | ( 0.58 - 3.01 )  |
| 3-7                                 | 128             | 71  | 2.90  | ( 1.39 - 6.04 )   | 30             | 67  | 0.99 | ( 0.43 - 2.29 )  |
| Ptrend                              |                 |     |       | <0.001            |                |     |      | 0.875            |
| <b>&gt;=10,000 drinks</b>           |                 |     |       |                   |                |     |      |                  |
| <b>Modified Fagerström</b>          |                 |     |       |                   |                |     |      |                  |
| 0                                   | 24              | 37  | 1.00  |                   | 31             | 89  | 1.00 |                  |
| 1-2                                 | 148             | 91  | 2.32  | ( 1.26 - 4.26 )   | 88             | 123 | 1.39 | ( 0.81 - 2.39 )  |
| 3-7                                 | 699             | 193 | 4.39  | ( 2.46 - 7.83 )   | 177            | 197 | 1.25 | ( 0.74 - 2.13 )  |
| Ptrend                              |                 |     |       | <0.001            |                |     |      | 0.627            |

\*Adjusted for center, education, sex, age, alcohol duration, alcohol frequency, and duration of smoking